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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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02/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,920	LEACH ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Clams 1-8 as amended (11/21/2008) are pending and under examination.

Claims 9-15 were canceled by applicants.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855).

Claims are directed to a method for culturing primary hepatocytes comprising steps of plating and culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent that inhibits the reactive species or increases intracellular glutathione, wherein said primary hepatocytes either maintain metabolic function or display fenestration for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent that increases intracellular glutathione or "glutathione precursor".

US 5,198,432 (Fariss) discloses a method for plating and culturing primary hepatocytes in Waymouth's medium (col.7, line 36) supplemented with antioxidant vitamin E including tocopherol succinate for 5-7 days on collagen surfaces (col. 14, lines 20-27). The Waymouth's

medium contains vitamins or antioxidants that are inhibitors of "reactive species within the broadest meaning of the claims (see ATCC catalogue page 525). The Waymouth's medium also contains folic acid that is an agent that increases intracellular glutathione as evidenced by Sharma et al. (page 5852). Thus, the method of US 5,198,432 (Fariss) for culturing primary hepatocytes comprises culturing primary hepatocytes in the presence of 2 agents within the broadest meaning of the claims. US 5,198,432 (Fariss) clearly states that hepatocytes remain viable for 5-7 days (col. 14, lines 20-27) and, thus, they are reasonably expected to maintain their metabolic activity such as metabolize xenobiotics to at least some extend.

Thus, the cited US 5,198,432 (Fariss) is considered to anticipate the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855) taken with Pourahmad et al. (IDS reference), Dilworth et al. (IDS reference) and Roberts et al. (IDS reference).

Claims are directed to a method for culturing primary hepatocytes comprising step of plating and culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent is a) a functional inhibitor of an enzyme that generates reactive

oxygen and reactive nitrogen species or b) an agent that directly inhibits the reactive species, or c) an agent that increases intracellular glutathione, wherein said hepatocytes either maintain metabolic function or display fenestration for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate or mannitol. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent such as glutathione precursor or "2-oxo-thiazolidine". Some claims are further drawn to culturing primary hepatocytes in the presence of the second agent such as inhibitor of nitric oxide or "NG-methylarginine". Some claims are further drawn to culturing primary hepatocytes in the presence of "2-oxo-thiazolidine" and tocopherol succinate as first and second agents. Some claims are further drawn to culturing primary hepatocytes in the presence of "NG-methylarginine" and mannitol as first and second agents.

US 5,198,432 (Fariss) teaches protective effects of antioxidants including tocopherol succinate on lifespan of cultures of primary hepatocytes. The cited method is relied upon as explained above for culturing primary hepatocytes including the use of Waymouth's medium supplemented with antioxidants or vitamins including tocopherol succinate and with agent increasing intracellular glutathione or folic acid as evidenced by ATCC Catalogue (page 525) and by Sharma et al. (page 5852). US 5,198,432 (Fariss) also discloses culturing hepatocytes on collagen matrices for 5-7 days in the protective medium.

The culture medium in the method of US 5,198,432 does not contain 2-oxo-thiazolidine, methylarginine and mannitol as first and/or protective second agents. However, the references teach protective effects of the presently claimed agents including mannitol (Pourahmad et al.), 2-

oxo-thiazolidine (Roberts et al.) and methylarginine (Dilworth et al.) on the cultures of hepatocytes, for example: see abstract of the cited references.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to incorporate protective agents including the presently claimed tocopherol succinate, 2-oxo-thiazolidine, methylarginine and/or mannitol in the culture of primary hepatocytes with a reasonable expectation of success in maintaining viability of hepatocytes because the presently claimed agents have been known and used for culturing and maintaining viability of hepatocytes as adequately demonstrated by the cited references combined. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 5/19/2008 have been fully considered but they are not persuasive.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and by Sharma et al. Applicants argue that US 5,198,432 (Fariss) does not teach that the primary plated hepatocytes maintain their function for at least 5 days and that in the cited method tocopherol is present in medium of hepatocyte suspension culture for 6 hour incubation period (response page 5). Upon review of the reference theses arguments are not found particularly persuasive. US 5,198,432 (Fariss) clearly discloses culturing primary hepatocytes (col. 14, line 23). US 5,198,432 (Fariss) clearly

teaches the protective effects of tocopherol (col. 14, line 20). The cited patent US 5,198,432 (Fariss) also states that hepatocytes remain viable for 5-7 days when cultured on matrix ("plated" hepatocytes as argued and as encompassed by the claims) instead of 8-12 hours as with suspension cultures, for example: see at col. 14, lines 20-29. The cited patent US 5,198,432 (Fariss) explicitly discloses the presence of tocopherol in suspension cultures (col.13, lines 60-65). Although the disclosure at (col.14, lines 20-30) might not be explicit with respect to the attached hepatocyte cultures, one of skill in the art would reasonably conclude or recognize that the culture media for both suspended and attached cultures were identical as it would be designed in a proper scientific experiment intended to compare suspended and attached cultures under influence of protective agents. Therefore, one of skill in the art would reasonably conclude that the primary hepatocytes attached to the matrix were cultured in the same medium comprising tocopherol as it was done for suspension cultures. Applicants appear to argue that table 10 at col. 14 recites only 6 hour incubation conditions. However, recitation about "6 hours" refers to the time interval for reading test results only and the recitation about 6 hours does not apply to the whole period or whole life time of hepatocyte culture. US 5,198,432 (Fariss) states that hepatocytes remain viable for 5-7 days when cultured on matrix under disclosed experimental conditions, wherein the disclosed experimental conditions include addition to tocopherol succinate to the base medium comprising folic acid ("second" agent that increases intracellular glutathione). Thus, the cited US 5,198,432 (Fariss) is considered to anticipate the presently claimed invention.

With regard to claim rejection under 35 USC § 103 applicants' main argument is that the cited references do not teach or suggest culturing hepatocytes for 5 days. This argument is not

found convincing since US 5,198,432 (Fariss) clearly states that hepatocytes remain viable for 5-7 days when cultured on collagen matrices instead of suspensions in the media with protective agents.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). All cited references are in the same field of endeavor and they seek to solve the same problems as the instant application and claims (such as culturing hepatocytes in the presence of protective agents), and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966). All presently claimed agents including tocopherol succinate, 2-oxo-thiazolidine, methylarginine and/or mannitol have been known and used for culturing and maintaining viability of hepatocytes as adequately demonstrated by the cited references combined. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. With respect to the claims 7 and 8 applicants did not present any arguments related to unobviousness of combination of particular ingredients.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

February 9, 2009

VERA AFREMOVA

PRIMARY EXAMINER

/Vera Afremova/
Primary Examiner, Art Unit 1657